

Colchicine as an Adjuvant Therapy for Coronary Artery Disease: A Systematic Review

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Abstract

Background: Inflammation plays a significant role in atherosclerosis at all phases. Colchicine is a pleiotropic anti-inflammatory agent that may be beneficial in various stages of coronary artery disease (CAD).

Methods: We searched for literatures in PubMed, Cochrane Library, ScienceDirect, and Proquest regarding the use of colchicine on top of current optimal medical therapy for CAD.

Results: Twelve studies were identified: three studies in stable CAD patients and the remaining nine assessed in acute coronary syndrome (ACS) and post-ACS patients. The majority of studies used a colchicine dose of 0.5 mg/day. Adjuvant colchicine of 0.5 mg daily reduced the risk of developing ACS, cardiac arrest, or ischemic stroke in stable CAD: Hazard Ratio 0.33 (95% CI 0.18-0.59), $p < 0.001$. Patients admitted with ACS who received a 2 mg loading dose of colchicine pre-percutaneous coronary intervention (PCI) showed smaller infarct size than control: 18.3 (IQR 7.6-29.9) ml/1.73 m² vs 23.2 (18.5-33.4) ml/1.73 m² ($p = 0.019$). In post-ACS patients, adjuvant colchicine of 0.5 mg daily significantly reduced the rate of ischemic cardiovascular events: HR 0.77 (95% CI 0.61-0.96), $p = 0.02$.

Conclusion: Current data suggest that colchicine might be beneficial for both acute and chronic CAD patients. This adjuvant therapy may reduce the composite rate of cardiovascular adverse outcomes in patients with established CAD.

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Introduction

The significant role of inflammation has been well-understood in the pathogenesis of atherosclerosis at every stage starting from plaque formation, progression, as well as plaque instability.¹⁻⁶ Over the last few years, there has been an increasing body of evidence that accentuates the deleterious effect of inflammatory processes in myocardial infarction. Since then, therapies specifically targeting inflammatory pathways have been postulated to be able to reduce vascular events in coronary artery disease (CAD).⁷ Statins, which are part of present-day optimal medical therapy in CAD, are known to confer a salutary effect on inflammation in addition to their lipid-lowering features. However, many patients still experience disease worsening despite statin consumption, leading to a current shift towards identifying another therapy that specifically targets inflammation.⁸ This effective and inflammation-specific medication for CAD is yet to be determined.⁹ Several biological, immunomodulatory and antioxidative therapies have been suggested. Lately, studies began to examine the potential role of colchicine adjuvant therapy in CAD patients. This pleiotropic anti-inflammatory drug has been administered to patients with gout & rheumatic problems, familial Mediterranean fever, and pericarditis.^{1, 5, 7} Colchicine is an inexpensive, relatively well-tolerated, orally administered, readily available anti-inflammatory agent that was initially extracted from the autumn crocus and has been utilized for centuries.^{1, 5, 6} It is able to interfere inflammatory processes by

inhibiting leukocyte migration and adhesion and suppressing key inflammatory signalling networks.^{1, 2, 5} Therefore, adding colchicine on top of current optimal medical therapy aims to further dampen inflammatory pathways of CAD in order to improve cardiovascular outcomes. Several clinical studies have been conducted to investigate the role of colchicine in CAD patients, yet results have been variable. Therefore, we aimed to elucidate the latest evidence regarding the role of colchicine as an adjuvant therapy in CAD patients.

Methods

Clinical studies for this systematic review were obtained via a search strategy and a selection process. We performed literature searching in 4 databases: PubMed, Cochrane Library, ScienceDirect, and ProQuest on February 3rd 2020; focusing on articles published in the last 5 years. We used Boolean technique to formulate the search terms used in each database, as shown by Table 1. Following that, a selection process was done to narrow down the search yield (Figure 1). We extracted information on study participants, modes of intervention, outcomes, and funding source of each article. Full text review of key papers also included screening of citations of relevant studies even if the studies were published earlier than the last 5 years. Three reviewers independently appraised all included articles for their risk of bias using the appraisal tool obtained from Centre for Evidence-Based Medicine Oxford University.

Table 1. Search strategy used in several databases conducted on February 3rd 2020

Database	Search Terms	Hits
PubMed	(colchicine [Title/Abstract/MeSH terms]) AND (((Acute coronary syndrome [Title/Abstract/MeSH terms]) OR Myocardial infarction [Title/Abstract/MeSH terms]) OR Atherosclerosis [Title/Abstract/MeSH terms])	135
Cochrane Library	((colchicine):ti,ab,kw AND ((acute coronary syndrome):ti,ab,kw OR (myocardial infarction):ti,ab,kw OR (atherosclerosis):ti,ab,kw)	74
ScienceDirect	Title, abstract, keywords: colchicine AND (acute coronary syndrome OR myocardial infarction OR atherosclerosis)	54
ProQuest	noft(Colchicine) AND (noft(acute coronary syndrome) OR noft(myocardial infarction) OR noft(atherosclerosis))	62

Search was conducted on February 3rd 2020

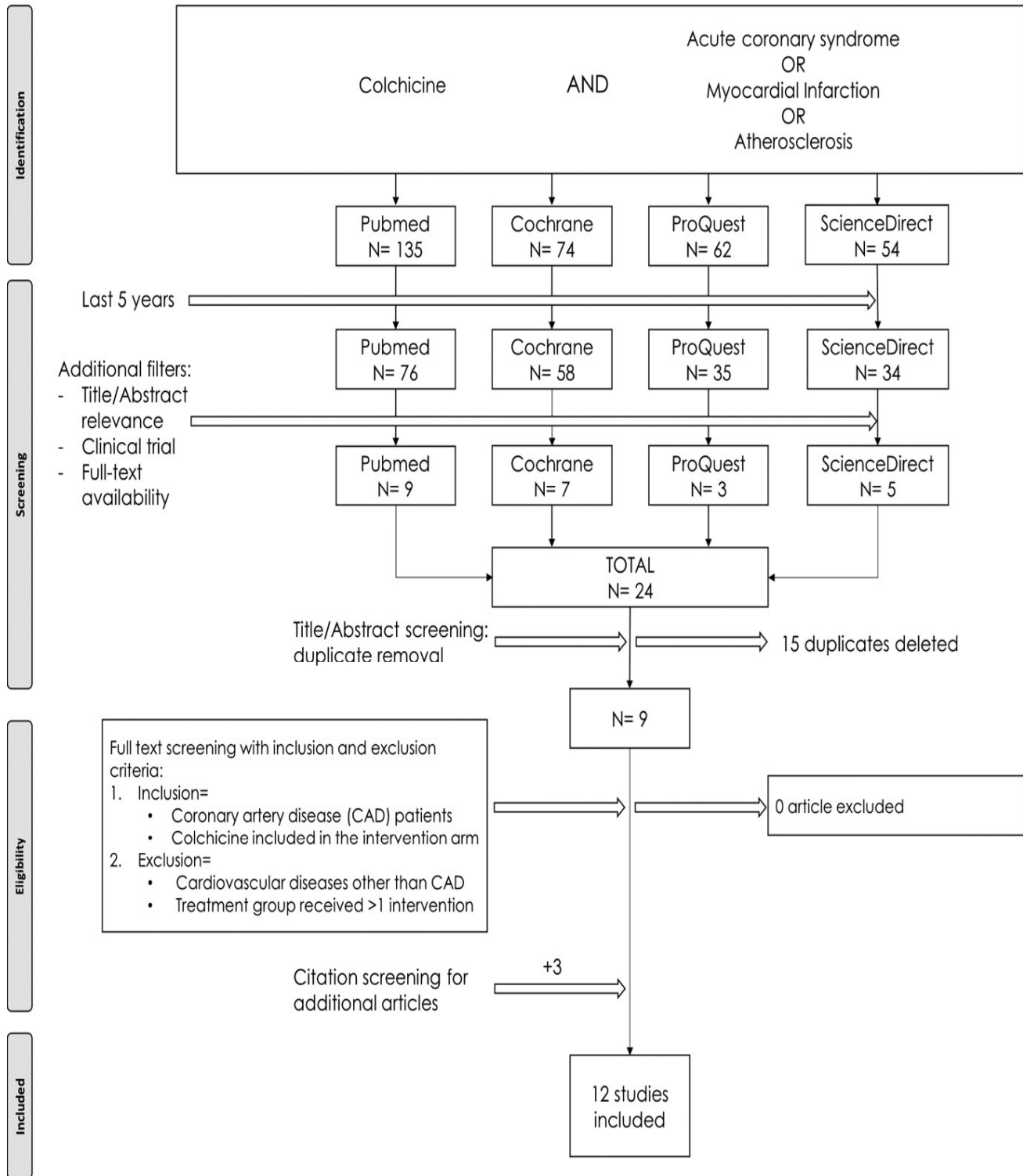


Figure 1. Selection flow chart. We included clinical studies administering patients to colchicine vs. placebo or no treatment on top of standard care. Eligible studies included adult patients with CAD including stable CAD, acute coronary syndrome (ACS), and recent ACS. No dose or treatment duration restrictions were used.

Result

In this systematic review, we searched for the current evidence regarding the role of colchicine as an adjuvant therapy in CAD patients. The initial search strategy yielded 325 records from 4 databases. After applying screening filters, 24 articles were identified of which 12 were retrieved for this systematic review. The 12 studies consisted of 2 non-randomized clinical trials, 4 pilot randomized clinical trials, and 6 randomized clinical trials. Prior to assessing the results of each study, we assessed the risk of bias in studies—including blinding of participants, randomization, allocation concealment, intention-to-treat analysis—which is displayed by Table 2.

The treatment allocation in seven of the studies was not concealed due to the absence of placebo usage. Only a minority of research groups were not kept blind during the course of some trials (3 out of 12) and two did not state clearly. Three studies did not produce clinically important nor statistically significant results. However, their results are still put into consideration in this review.

All studies are considered applicable as the drug regimen used is readily available. As for the funding, no study received a funding source from pharmaceutical companies. Only 1 study (Hennessy *et al.*) received free colchicine and placebo from a pharmaceutical company.

The study population, treatment dose, treatment duration, and the outcomes differ among clinical trials. Three studies evaluated the effect of colchicine on stable CAD patients and the remaining 9 assessed on acute coronary syndrome (ACS) and post-ACS patients. While the majority of studies used a colchicine dose of 0.5 mg/day, some studies administered 1 mg/day and even a loading dose of 2 mg. As for the outcome measures, 4 studies assessed the effect of colchicine by means of radiographic modalities and 9 studies utilized various forms of evaluation mode to assess the degree of inflammation. Five studies measured inflammatory response through circulating C-reactive protein (CRP), 2 studies measured inflammatory mediators, and 2 studies assessed for long-term cardiovascular outcomes. The duration of treatment and follow-up period widely varied, ranging from 24 hours to 3 years. The imaging modalities were also heterogenous among studies,

Table 2 Critical appraisal of included studies.

Author	Year of publication	Study design	Number of participants	Level of evidence	Randomization	Allocation concealment	Intention-to-treat	Blinding	Comparable treatment	Similarity treatment & control	Clinical importance	Statistical significance*	Precision of treatment effect	Feasibility of treatment	Benefit outweighs harm
Nidorf, et al.(10)	2007	Clinical trial	64	2	-	-	+	-	+	+	+	+	-	+	+
Raju, et al.(11)	2012	Pilot RCT	80	2	+	+	+	+	+	+	-	-	+	+	+
Nidorf, et al.(12)	2013	RCT	530	1	+	-	+	+	+	+	+	+	+	+	+
Deftereos, et al.(13)	2015	Pilot RCT	151	2	+	+	-	+	+	+	-	+	-	+	+
Martínez, et al.(3)	2015	RCT	83	1	+	-	+	?	+	+	+	+	+	+	+
Robertson, et al.(4)	2016	RCT	21	1	+	-	+	?	?	+	+	+	-	+	+
Akodad, et al.(1)	2016	RCT	44	2	+	-	+	-	+	+	-	-	-	+	+
Vaidya, et al.(6)	2017	Clinical trial	80	2	-	-	+	-	?	+	+	+	-	+	+
Kajikawa, et al.(2)	2019	RCT	28	2	+	+	+	+	?	+	-	+	-	+	+
Hennessy, et al.(7)	2019	Pilot RCT	222	2	+	+	+	+	+	+	-	-	-	+	+
Tucker, et al.(14)	2019	Pilot RCT	25	2	+	-	+	+	+	+	+	+	+	+	+
Tardif, et al.(5)	2019	RCT	4458	1	+	+	+	+	+	+	+	+	+	+	+

+ present; - absent; ? not mentioned/ unclear; *significance at p<0.05

including coronary computed tomography (CT) angiography, ultrasonography, and cardiac magnetic resonance imaging (CMR).

Colchicine given 0.5 mg daily for 3 years improved cardiovascular outcomes of patients with stable CAD in terms of reducing the risk of developing ACS, cardiac arrest, or ischemic stroke: Hazard Ratio 0.33 (95% CI 0.18-0.59), $p < 0.001$. CRP was significantly lower in the treatment group: 1.78 ± 1.23 vs 3.7 ± 2.3 mg/L, $p < 0.002$. Patients admitted with ACS who received a 2 mg loading dose of colchicine pre-percutaneous coronary intervention (PCI) showed smaller infarct size than control: 18.3 (interquartile range (IQR) 7.6-29.9) ml/1.73 m² vs 23.2 (IQR 18.5-33.4) ml/1.73

m² ($p = 0.019$). However, CRP reductions were similar between the 2 groups. In post-ACS patients, colchicine 0.5 mg daily significantly reduced the incidence of future ischemic cardiovascular events after given for a median of 20 months: HR 0.77 (95% CI 0.61-0.96), $p = 0.02$. Furthermore, patients with recent ACS who received 0.5 mg of colchicine daily displayed a reduction in volume of low attenuation plaque (LAP) on coronary CT angiography after 1 year: -41% vs -17% , $p = 0.008$. More details of the publications namely trial authors, enrolment period, year of publication, description of the interventions used, and outcomes are summarized in Table 3.

Table 3 Findings summary of studies evaluating colchicine in CAD

Investigator	Primary site(s), enrolment period	Study design	Study population	Sample size	Intervention	Control	Mode of inflammation evaluation	Outcome
Nidorf, et al. (2007)	Not mentioned	Non randomized	Stable CAD (confirmed with diagnostic imaging)	64 patients: 44 colchicine and 20 no colchicine	Colchicine 2 x 0.5 mg for 1 month plus standard care (aspirin, atorvastatin)	Standard care (aspirin and atorvastatin)	CRP	Follow-up at 1 month. Decreased mean hs-CRP was obtained at day 30: 4.53 ± 2.10 mg/L (baseline) to 1.78 ± 1.23 mg/L, $p < 0.001$. At day 30, hs-CRP of treatment group was 1.78 ± 1.23 mg/L vs control 3.7 ± 2.3 mg/L, $p < 0.002$
Raju, et al. (2012)	Hamilton General Hospital Hamilton, Ontario, Canada; from April 2008 to August 2009	RCT	ACS and acute ischemic stroke patients	80 patients: 40 colchicine and 40 placebo	Colchicine 1 x 1 mg for 1 month plus standard care (DAPT, statin)	Placebo 1 x 1 mg for 1 month plus standard care (DAPT, statin)	CRP	Mean duration of follow up was 31 days (SD 17 days). Colchicine did not significantly reduce hs-CRP at day 30 (1.0 vs 1.5 mg/L, $p = 0.22$) nor reductions of hs-CRP from baseline (7.0 vs 7.1 mg/L, $p = 0.64$).

Nidorf, et al. (2013)	Sir Charles Gairdner Hospital, Perth, Western Australia; from August 2008 to May 2010	RCT	Stable CAD (confirmed with diagnostic imaging)	530 patients: 282 colchicine and 250 no colchicine	Colchicine 1 x 0.5 mg for 3 years (median), plus standard care (DAPT, statin, β -blocker, ACE-I)	Standard care (DAPT, statin, β -blocker, ACE-I)	N/A	Follow up for up to 44 months. Composite incidence of ACS, out-of-hospital cardiac arrest, or non-cardioembolic ischemic stroke occurred in 15 of 282 patients (5.3%) in treatment group and 40 of 250 patients (16.0%) who did not receive colchicine: HR 0.33 (95% CI 0.18-0.59) $p < 0.001$
Deftereos, et al. (2015)	Athens General Hospital "G. Gennimatas" Athens, Greece; from July 2013 to March 2015	RCT	STEMI treated with PCI	151 patients: 77 colchicine and 74 placebo	Colchicine loading dose 2 mg immediately before reperfusion (1.5 mg + 0.5 mg 1h later) and continuing 2 x 0.5 mg daily for 5 days plus standard care (DAPT, statin, β -blocker)	Placebo for 5 days plus standard care (DAPT, statin, β -blocker)	N/A	Follow-up for up to 9 days. The AUC of 5-day CK-MB was significantly lower in treatment group: 3144 (1754-6940) ng.h/ml vs 6184 (4456-6980) ng.h/ml, $p < 0.001$. Infarct size, determined by CMR, was smaller in the colchicine group: 18.3 (IQR 7.6-29.9) ml/1.73 m ² vs 23.2 (18.5-33.4) ml/1.73 m ² , $p = 0.019$. The relative infarct size as a proportion of left ventricle myocardial volume was also smaller in colchicine group: 13% (IQR 8.0-25.3)% vs 19.8% (IQR 13.7-29.8)%, $p = 0.034$.
Martínez, et al (2015)	Royal Prince Alfred Hospital (Sydney, NSW, Australia; from September 2013 to August 2014	RCT	ACS (other than STEMI), stable CAD	83 patients: 40 ACS (21 colchicine, 19 no colchicine), 33 stable CAD (13 colchicine, 20 no colchicine), 10 healthy controls	Colchicine 1 mg + 0,5 mg 1h later (6-24 hours prior to coronary angiography), 2500 U heparin prior to coronary sinus sampling. Standard care (DAPT, statin, β -blocker, ACE-I)	(DAPT, statin, β -blocker, ACE-I)	Interleukin	Blood samples were drawn during cardiac catheterization. In comparison to ACS patient without colchicine and controls, ACS patients who received colchicine displayed a significant reduction of coronary sinus IL-1 β , gradient IL-1 β , gradient IL-18, coronary sinus IL-6, and gradient IL-6 ($p < 0.05$), but no significant difference in coronary IL-18 ($p = 0.239$). No significant difference in stable CAD groups with vs without colchicine vs control (all $p > 0.05$)

Kajikawa, et al (2019)	2 general hospitals in Japan; from April to December 2015	RCT	CAD history confirmed with diagnostic imaging	28 patients: 14 colchicine, 14 placebo, washout for at least 14 days, crossover within subjects	Colchicine 1 x 0,5 mg for 7 days, standard care not mentioned	Placebo 1 x 0.5 mg for 7 days, standard care not mentioned	CRP FMD and blood samples were measured at day 7 post-treatment. No significant difference in endothelial function: 3.1% (IQR 1.5–5.3%) vs. 3.3% (IQR 1.9–5.2%), p=0.384. Serum hs-CRP levels were significantly reduced in colchicine group in comparison with the placebo group: 0.04 (IQR 0.02–0.08) mg/dL vs. 0.07 (IQR 0.04–0.11) mg/dL, p= 0.003].
Hennessy, et al (2019)	Royal Perth Hospital, Perth, Western Australia; from February 2016 to July 2017	RCT	Acute MI within the last 7 days (90% had PCI during index admission)	222 patients: 111 colchicine and 111 placebo	Colchicine 1 x 0.5 mg for 30 days plus standard care (DAPT, statin, β -blocker, ACE-I)	Placebo 1 x 0.5 mg for 30 days plus standard care (DAPT, statin, β -blocker, ACE-I)	CRP Follow-up for 1 month. Baseline CRP was similar in both groups (p=0.77). At day 30, the proportion of patients with CRP level ≥ 2 mg/L was 44% in colchicine group and 50% in placebo group (p=0.35).
Tucker; et al (2019)	Royal Prince Alfred Hospital (Sydney, NSW, Australia); from March 2017 to October 2017	RCT	ACS, stable CAD	25 ACS patients: 12 colchicine, 13 no colchicine; and 13 stable CAD	Colchicine 1 mg + 0.5 mg (1h later), 6 to 24 hours before undergoing cardiac catheterization	Standard care (aspirin, statin, β -blocker, ACE-I)	Chemokines Blood samples were drawn during cardiac catheterization. Colchicine treatment markedly reduced transcoronary levels of CCL2, CCL5, and CX3CL1 in patients with ACS (p< 0.05) compared to ACS with standard care.

Tardif et al. (2019)	Montreal Heart Institute Montreal, Quebec, Canada; from December 2015 to August 2018	Acute MI within the last 30 days (mean 13.5 days; with 93% of total underwent PCI).	4458 patients: 2226 colchicine and 2232 placebo	Colchicine 1 x 0.5 mg for a median of 19.6 months, plus standard care (DAPT, statin, β -blocker,	Placebo 1 x 0.5 mg for a median of 19.5 months, plus standard care (DAPT, statin, β -blocker, revascularization)	Follow-up for a median of 23 months. The number of incidence of the first ischemic cardiovascular event (composite of cardiovascular death, resuscitated cardiac arrest, acute MI, stroke, or urgent hospitalization for angina requiring coronary revascularization) from randomization was 131 (5.5%) treatment group vs. 170 (7.1%) control group; HR 0.77 (95% CI 0.61-0.96); p=0.02. The components of primary end point: cardiovascular death: 20 (0.8%) vs. 24 (1.0%); HR 0.84 (0.46-1.52), p=NS; resuscitated cardiac arrest: 5 (0.2%) vs. 6 (0.3%); HR 0.83 (0.25-2.73); myocardial infarction: 89 (3.8%) vs. 98 (4.1%); HR 0.91 (0.68-1.21); stroke: 5 (0.2%) vs. 19 (0.8%); HR 0.26 (0.10-0.70), p<0.05; urgent hospitalization for angina leading to revascularization: 25 (1.1%) vs. 50 (2.1%); HR 0.50 (0.31-0.81), p<0.05.
		RCT				N/A

Abbreviations: ACE-I angiotensin converting enzyme inhibitor, ACS acute coronary syndrome, AUC area under curve, CAD coronary artery disease, CCL2 chemokine ligand 2, CCL5 chemokine ligand 5, CK-MB creatine kinase-MB, CMR cardiac magnetic resonance imaging, CX3CL1 C-X3-C motif chemokine ligand 1, CRP C-reactive protein, DAPT dual antiplatelet therapy, Hazard Ratio, hs-CRP high sensitivity C-reactive protein, IL interleukin, LAP low attenuation plaque, LDL low density lipoprotein, mRNA messenger RNA, MI myocardial infarction, NS not significant, RCT randomized controlled trial, SD standard deviation, STEMI ST-elevation myocardial infarction.

Discussion

CAD patients are still at risk of developing future acute cardiovascular events in spite of routine use of antiplatelet and statin therapy. This phenomenon might be attributable to the presence of some of the inflammatory pathways implicated in the disease that are not targeted by standard therapies.¹² A monoclonal antibody specifically targeting IL-1 β , canakinumab, has been previously studied. It was found to be able to modestly lower the risk of cardiovascular mortality.⁹ Unfortunately concerns were evoked after looking at the higher rate of fatal infections caused by this treatment.⁹ Another anti-inflammatory agent, methotrexate, displayed no cardiovascular outcome benefit.⁹ The beneficial effect of colchicine on cardiovascular was previously seen from 2 retrospective studies, in which

a reduced incidence of cardiovascular death was found in patients receiving continuous colchicine use for the therapy of familial Mediterranean fever and gout.^{6, 12} Therefore, in this review we examined whether colchicine has a direct impact in suppressing inflammatory pathways in atherosclerosis, and ultimately whether it is beneficial as an adjuvant therapy for CAD patients.

Colchicine as an anti-inflammatory agent

As mentioned previously, atherosclerosis has a very close relationship with inflammation. CRP, an inflammatory biomarker, correlates strongly with prognosis in CAD patients, both in stable CAD, ACS, and post-ACS patients. It has been previously reported that stable CAD patients with high sensitivity CRP (hs-CRP) levels above 2.0 mg/L would have a higher risk of future vascular events.¹⁰ At the event of an ACS, a

systemic biological response of inflammation ensues. A peak of CRP level (usually around day 3) is recognized as a prognostic marker due to its correlation with infarct size¹, and left ventricular remodelling.¹³ In patients with recent ACS, increased baseline hs-CRP levels were independently associated with an increased risk of recurrent infarctions and death due to coronary heart disease.^{7,11}

Among the studies reviewed, there were 5 studies that assessed the effect of colchicine on CRP: four in ACS patients and one in stable CAD (Figure 2 A-C). Overall in ACS, CRP absolute or relative reduction differences were not found to be statistically significant between treatment and control groups.^{1,7,11} Meanwhile, colchicine was able to significantly decrease both absolute and Δ CRP levels in stable CAD patients (a difference of ± 2 mg/L).¹⁰ This result discrepancy could be explained by the absence of a larger loading dose in studies assessing ACS patients.¹ As an analogy, a patient with acute gout would require a much larger dose of colchicine to suppress the higher degree of inflammation during acute attack in comparison to a rather stable hyperuricemia. Low doses are still effective in the suppression of the low-grade inflammation, which is a feature of chronic atherosclerosis.¹¹ Therefore, this may explain the significant difference in stable CAD patients, while the contrary was found in ACS patients.

Furthermore, the lack of effect may also be explained by the late administration of colchicine following reperfusion. Devereux *et al.* found that a loading dose of colchicine administered to patients with ST elevation myocardial infarction (STEMI) undergoing primary PCI was able to decrease infarct size evaluated through biomarker release (i.e.: creatinine kinase-MB) and cardiac magnetic resonance imaging (CMR).¹³ In the study by Akodad *et al.*, no significant difference was found in cardiac remodeling assessed by CMR in patients with similar baseline characteristics however without a loading dose of colchicine pre-PCI.¹ Prompt treatment after acute MI is therefore required in early reduction of pro-inflammatory pathways. This further emphasizes the fact that treatment should be given at the onset of reperfusion, as soon as possible, in order to optimize its action and to reduce reperfusion injuries associated with inflammation burden.¹

The duration of colchicine treatment may also affect the outcome. Among the ACS patients who received

treatment, short-term administration of colchicine for a duration of one month^{1,7,11} may be insufficient to dampen overt inflammation in patients with acute atherothrombosis. Compared to the study by Vaidya *et al.*⁶: after multivariate analysis, colchicine therapy remained significantly associated with a reduction in hs-CRP after 1 year of treatment (Figure 2 A and B).

Lastly, another reason for the lack of effect of colchicine on CRP in ACS patients is that a causal role of hs-CRP in the pathogenesis of atherothrombosis is not proven and that colchicine may only inhibit some of the numerous pathways pertaining to hs-CRP elevation following an acute vascular event.¹¹

Other markers of inflammation are those directly involved in the inflammatory process itself. ACS patients who were given colchicine within 24 hours before cardiac catheterization significantly displayed a reduction in local synthesis of IL-1 β , IL-18, and IL-6.³ Additionally, Tucker *et al.* found that colchicine administration acutely suppressed local cardiac production of chemokine ligand 2 (CCL2), chemokine ligand 5 (CCL5), and C-X3-C motive chemokine ligand 1 (CX3CL1).¹⁴ The acute suppression of these pro-inflammatory cytokines and the reduction in intracardiac chemokine expression in ACS patients have potentially important therapeutic implications.³ Not only the acute process of a myocardial infarction itself, even the therapy of reperfusion could also aggravate the inflammation-mediated injury by allowing free oxygen radicals to flow through.¹ Therefore, acute inhibition of a number of key inflammatory cascade effectors with the use of pre-PCI colchicine may lead to a decrease in inflammation, which results in a smaller infarct size. This explains the correlation found between the results of the studies conducted by Martinez *et al.*³ and Tucker *et al.*¹⁴, with a smaller infarct size evidenced by Devereux *et al.*¹³, all of which administered a loading dose of colchicine prior to catheterization or PCI (Figure 2 A and B). A significant proportion of post-ACS patients still manifest biomarkers of ongoing inflammation, most likely propelled by a pan-vascular inflammation despite current guideline-based therapy, and therefore remain at a relatively high risk of recurrent vascular events.^{4,8,10,12} Therefore, due to the systemic anti-inflammatory effects of colchicine, this agent has a potential to stabilize both culprit and non-culprit lesions, leading to a reduction in the incidence of new vascular events post-ACS.³

Colchicine as a plaque stabilizer

Vulnerable, rupture-prone plaques are commonly rich in lipid content, with a large necrotic core and covered by a thin fibrous cap.⁶ This type of plaque can be distinguished on coronary CT angiography by the identification of outward vessel positive remodelling and LAP.⁶ In turn, LAP has been consistently shown to be the best plaque instability marker and the strongest predictor of a future acute cardiovascular event.⁶ Vaidya

et al. found a reduction in all coronary CT angiography plaque parameters of interest (LAP volume, dense calcified plaque volume, noncalcified plaque volume, and total atheroma volume) in the treatment group, with statistically significant reductions in LAP volume even after multivariate analysis.⁶ It is important to note that the coronary CT angiography parameters between groups at baseline were comparable and these changes were seen in subjects consuming statin. Given that both groups had comparable reductions of low density

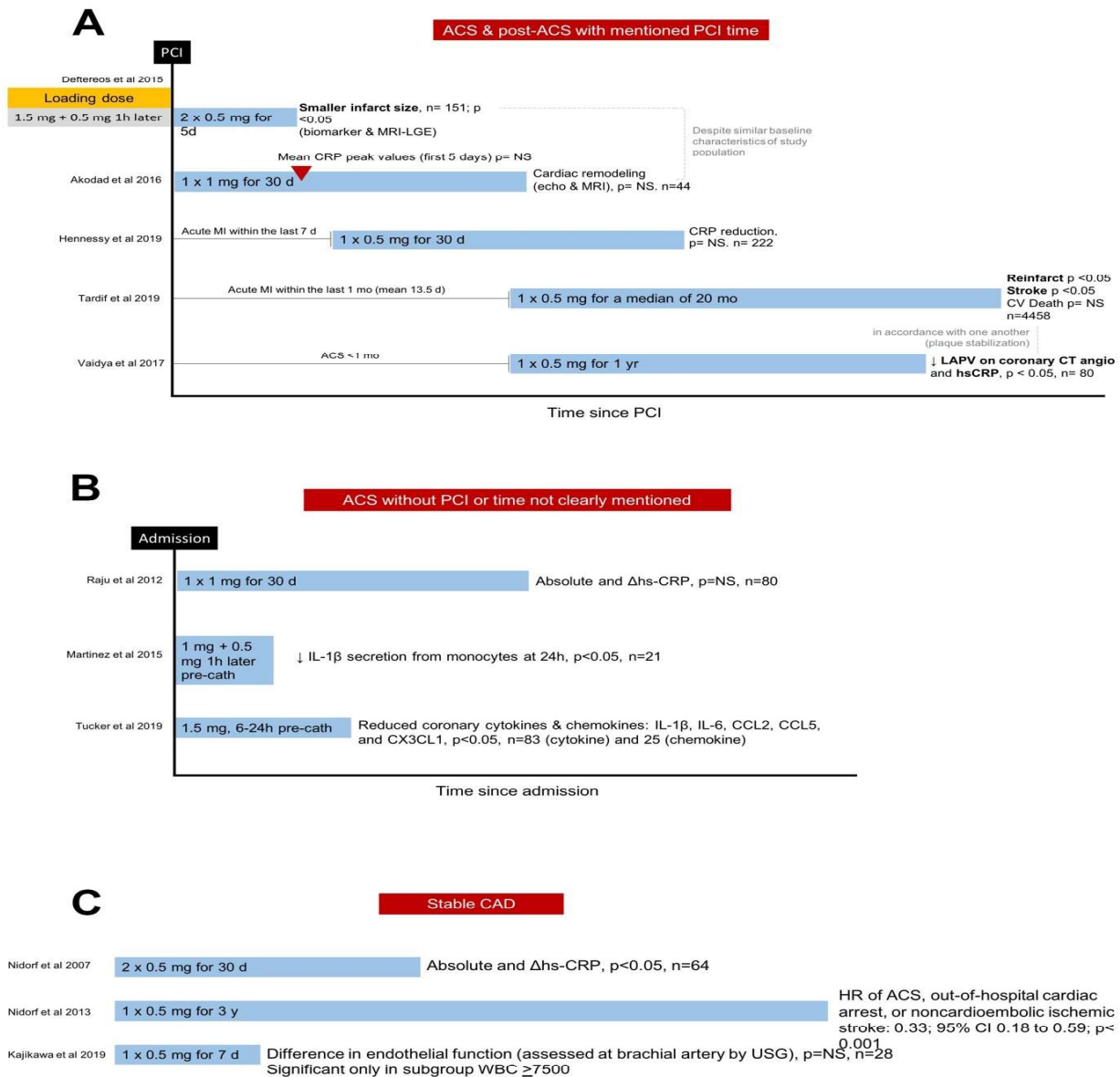


Figure 2. Colchicine doses and treatment durations among studies grouped into A) ACS & post-ACS with specified PCI time B) ACS without specified PCI time, and C) stable CAD.

lipoprotein (LDL) levels and even statin use was lower in the treated group, it could be implied that plaque stability and morphology improvements were not exclusively mediated by statin, but also by colchicine.⁶

According to Nidorf *et al.*, who studied subjects with stable CAD over a median of three years, the administration of colchicine 0.5 mg/day administered in addition to high-dose statin therapy and other optimal medical therapy was highly effective in the prevention of ACS compared to the placebo group.¹² This finding is in accordance with the study conducted by Vaidya *et al.* suggesting a possible plaque-stabilizing property of colchicine. Of note, these studies used colchicine for a longer period of time: one year and three years respectively (Figure 2 A and C). Kakijawa *et al.* conducted a study on stable CAD and the effect of colchicine on endothelial dysfunction, a process involved in the initial development of atherosclerosis, through flow-mediated vasodilation (FMD). FMD is an indicator of endothelium-dependent vasodilation and this parameter has been widely used to evaluate endothelial function.² Unfortunately the study only observed a short-term effect of colchicine (7 days) and was evaluated from the brachial artery, indicating that the results may or may not reflect the coronary situations.

Colchicine and cardiovascular outcomes

Two studies evaluated the effect of colchicine on cardiovascular outcomes: one in ACS patients and the other in stable CAD patients (Figure 2 A and C). ACS is associated with higher risks of recurrent events and exacerbated inflammation. Tardif *et al.* evaluated the long-term effects of colchicine in recent post-ACS patients.⁵ Their results showed that lower ischaemic cardiovascular events was predominantly due to a lower incidence of urgent hospitalizations for angina that needs coronary revascularization and stroke.⁵ However, no significant difference on cardiovascular-related mortality was observed in that study. This may be due to complications of ACS, namely heart failure development, given that no loading dose of colchicine was administered at the onset of ACS that might reduce infarct size. As for the stable CAD patients, Nidorf *et al.*¹² found that colchicine adjuvant therapy was able to reduce the risk of getting future cardiovascular events, mainly by preventing of ACS development from stable atherosclerotic plaque.

These findings further support colchicine's role as an anti-inflammatory agent and as a plaque stabilizer to prevent ACS in CAD patients and recurring infarcts in post-ACS patients. However, it is important to note that results were observed against a background of appropriate medications—including dual antiplatelets, statin, and revascularization strategies when necessary—suggesting that colchicine is an adjuvant therapy.

Tolerability

Expanding the indication of existing drugs for another diseases is a savvy way to improve medical care for at least three reasons.¹⁵ First, these generic drugs are more affordable in comparison to newer generation drugs. Second, their safety profile has been established for years. Third, the medical community is already familiar with these drugs, meaning that its use does not necessitate highly specialised centers, rendering general and family practitioners to be able to use them.¹⁵

To evaluate tolerability, we looked at the responses from patients with long-term use of colchicine namely in studies by Nidorf *et al.*¹², Vaidya *et al.*⁶, and Tardif *et al.*⁵ Generally, colchicine was well tolerated with no serious toxicity, however it was associated with gastrointestinal upset in a proportion of subjects. Diarrhea was reported in 9.7% of patients in the colchicine group and in 8.9% of subjects in the placebo group ($p=0.35$).⁵ Additionally nausea was more common in the colchicine group than in the placebo group (1.8% vs. 1.0%, $p=0.02$).⁵ Pneumonia was reported as a serious adverse event in 0.9% of the patients in the colchicine group, compared to 0.4% of subjects in the placebo group ($p=0.03$).⁵ In the study by Vaidya *et al.*, only one patient developed diarrhea as a result of colchicine therapy.⁶ Nidorf *et al.*¹² reported side effects including gastrointestinal upset (seven patients), myalgia (two patients), myositis (one patient), rash (one patient), alopecia (one patient), itch (one patient), and peripheral neuritis (one patient).

It has been noted that colchicine, while seems to be a promising anti-inflammatory agent for CAD, often generates some side effects. Colchicine is derived from *Colchicum autumnale*. This drug is mainly metabolized in the gastrointestinal tract with its frequent side effect being gastrointestinal upset. Some reported that gastrointestinal side effects appear in 5-10% of patients¹⁶ although it may occur as high as >20% in other report¹⁷. The symptoms include nausea,

vomiting, abdominal pain, and diarrhea^{16,18}. Diarrhea is reported to be the most common side effect and can cause cessation of colchicine therapy¹⁸. Gastrointestinal symptoms are said to be dose-dependent, and thus may improve by lowering the administered dose¹⁷. Taking this medication with or after food may also ease gastrointestinal symptoms¹⁹. However, it is important to note the narrow therapeutic index of colchicine with sometimes overlapping therapeutic and toxic doses in some cases. Gastrointestinal symptoms may alarm colchicine toxicity since its earliest toxicity symptoms typically present as gastrointestinal problems. The lowest reported fatal dose for oral administered Colchicine ranged between 7-26 mg²⁰. Management of toxicity include determination of the dose ingested or administered, immediate gastrointestinal cleansing, and aggressive supportive care such as anti-emetics and activated charcoal administration²⁰⁻²²

It is important to note that the combination of colchicine with statin therapy could increase the risk of myalgia.¹² Despite these caveats, colchicine is still an attractive prospect therapy for secondary prevention of cardiovascular events mainly due to its simple administration, affordability, and wide availability. From this review, we can see that the long-term use of colchicine at doses of 1 to 2 mg/day is safe and reasonably well-tolerated.

Future Studies

In this review it is shown that patients with stable CAD, ACS, and even patients with recent post-ACS benefit from colchicine adjuvant therapy. However, future studies need to better delineate potential benefit across CAD patient subgroups so that a more personalized treatment regimen can be planned. Generally, administering multiple drugs to a patient has the potential to lower treatment adherence. There are several ongoing studies evaluating colchicine use in patients with CAD. We searched for ongoing trials of colchicine use in CAD Clinicaltrials.org and World Health Organization (WHO) International Clinical Trials Registry Platform and found several studies:²³⁻²⁸. It is hoped that these studies will further identify specific CAD subgroup(s) that benefit from colchicine adjuvant therapy.

Conclusion

On a background of standard CAD therapy, the addition of colchicine may provide an additional advantage for both acute and chronic CAD patients in terms of reducing the composite rate of cardiovascular adverse outcomes in patients with established CAD.

Limitation

Some of the data presented in this review are presented as interquartile range, indicating an abnormal data distribution that is used to synthesize our results. In addition, some studies are pilot RCT which could raise a concern that analyses were taken too early to generate meaningful results. Lastly, the anticipated anti-inflammatory outcome from colchicine therapy were assessed through a wide range of inflammatory marker, leading to a non-uniform result.

Publication Approval

All authors read and approved the final manuscript

Conflict of interest

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Ethical Clearance

Not Applicable

List of abbreviations:

ACE-I: angiotensin converting enzyme inhibitor
 ACS: acute coronary syndrome
 AUC: area under curve
 CAD: coronary artery disease
 CCL2: chemokine ligand 2
 CCL5: chemokine ligand 5
 CK-MB: creatine kinase-MB
 CMR: cardiac magnetic resonance imaging
 CX3CL1: C-X3-C motif chemokine ligand 1
 CRP: C-reactive protein
 DAPT: dual antiplatelet therapy
 HR: hazard ratio

hs-CRP: high sensitivity C-reactive protein
 IL: interleukin
 IQR: interquartile range
 LAP: low attenuation plaque
 LDL: low density lipoprotein
 MI: myocardial infarction
 mRNA: messenger RNA
 NS: not significant
 RCT: randomized controlled trial
 SD: standard deviation
 STEMI: ST-elevation myocardial infarction.

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